

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



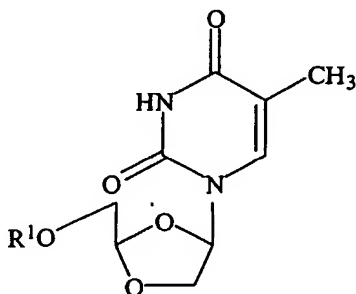
(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052296 A3

- (51) International Patent Classification⁷: A61K 31/70, 31/65, 31/52, 31/505
- (21) International Application Number: PCT/US2003/039029
- (22) International Filing Date: 8 December 2003 (08.12.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/431,812 9 December 2002 (09.12.2002) US
- (71) Applicants (*for all designated States except US*): THE UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. [US/US]; Boyd Graduate Studies Research Center, Athens, GA 30602-7411 (US). EMORY UNIVERSITY [US/US]; 1380 South Oxford Road, Atlanta, GA 30322 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): CHU, Chung, K. [US/US]; 115 Cedar Springs Place, Athens, GA 30605 (US). SCHINAZI, Raymond, F. [US/US]; 1524 Regency Walk Dr., Decatur, GA 30033 (US).
- (74) Agent: HENRY, Coleman, D.; Coleman Sudol Sapone, P.C., 714 Colorado Avenue, Bridgeport, CT 06605-1601 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report: 23 September 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: DIOXOLANE THYMINE AND COMBINATIONS FOR USE AGAINST 3TC/ AZT RESISTANT STRAINS OF HIV



(I)

(57) Abstract: The present invention relates to the use of a dioxolane thymine compound according to the chemical structure of Formula (I): where R¹ is H, an acyl group, a C₁-C₂₀ alkyl or ether group, a phosphate, diphosphate, triphosphate or phosphodiester group, for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. Preferably, compounds according to the present invention are combined with at least one anti-HIV agent which inhibits HIV by a mechanism other than through the inhibition of thymidine kinase (TK). These agents include those selected from among nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, among others. These agents are generally selected from the group consisting of 3TC (Lamivudine), AZT (Zidovudine), (-)-FTC, ddI (Didanosine), ddC

(zalcitabine), abacavir (ABC), tenofovir (PMPA), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), EFV (Efavirenz), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), fuseon and mixtures thereof. The TK dependent agents, such as AZT and D4T, may be used in combination with one of the dioxolane thymine compounds according to the present invention, but the use of such agents may be less preferred. In preferred compositions according to the present invention, R¹ is preferably H or a C₂-C₁₈ acyl group or a monophosphate group. Pharmaceutical compositions and methods of reducing the likelihood that a patient at risk for contract an HIV infection will contract the infection are other aspects of the present invention.

WO 2004/052296 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/39029

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/70, 31/65, 31/52, 31/505

US CL : 514/50, 152, 262, 274

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/50, 152, 262, 274

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, West, Palm: inventor, compounds, antiviral methods, HIV, retroviral

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,270,315 A (BELLEAU ET AL) 14 December 1993 (14.12.93), see compound VI, column 6.	1-4, 30-34, 41-44 ----- 5, 12-17, 20, 21, 23-29, 35-40
--- Y	US 5,047,407 A (BELLEAU ET AL) 10 September 1991 (10.09.91), see columns 1-8.	1-5, 12-17, 20, 21, 23-44
--- Y	CHU et al. Enantiomeric Synthesis of (+)-BCH-189 [(+)-(2S,5R)-1-[2-(Hydroxymethy.)-1)-1,3-oxathiolan-5-yl]cytosine] from D-Mannose and Its Anti-HIV Activity, J. Org. Chem. 1991, Vol. 56, No. 23, pages 6503-6505, 199, see figure 1, and page 6505.	1-5, 12-17, 20, 21, 23-44



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

21 April 2004 (21.04.2004)

Date of mailing of the international search report
01 JUL 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 872-9306

Authorized officer

Russell Travers

Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/39029

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 6-11, 18, 19 and 22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.